REMARKS

Claims 1-37 are pending in this application. Claim 23 has been amended as shown in Appendix A to recite a specific embodiment of the invention. The claims pending upon entry of the amendment are attached hereto as Appendix B. No new matter has been added.

I. The Rejections Under 35 U.S.C. §112 Should be Withdrawn

On page 4 of the Office Action, claims 13-20, 22, 29-32, 35, 37 are rejected under the second paragraph of §112, allegedly because "it is not clear whether the conditions required for the DISSOLUTION TEST in the specification at page 18 remain constant or if they may change over time." This rejection is traversed for the following reasons.

The conditions of the DISSOLUTION TEST are clearly defined in the specification. *See* page 18, lines 9-16. For example, line 13 states "two tablets in 100mL of water"; lines 11-12 state "water at 19°C - 21°C"; and lines 15-16 state "must pass through a screen with a nominal mesh of 710 microns." These conditions are constant, and Applicants respectfully submit that one of skill in the art would consider them to be so. Because it is a well-established principle of patent law that the meanings of the claims are to be interpreted in light of the specification, Applicants respectfully submit that the scope of each of the claimed embodiments of the invention is particularly and clearly recited. Manual of Patent Examining Procedure (M.P.E.P.) § 2173.05(a) (citing *In re Zletz*, 893 F.2d 319 (Fed. Cir. 1989)). Further, it is clear that the claims are interpreted as one of ordinary skill in the art would have understood them at the time of the invention. *See, e.g., Interconnect Planning Corp. V. Feil* 774 F.2d 1132, 1138 (Fed. Cir. 1985). Applicants therefore respectfully request that the rejection of claims 13-20, 22, 29-32, 35, 37 be withdrawn.

II. The Rejection Under 35 U.S.C. 102(e) Should be Withdrawn

On page 2 of the Office Action, independent claim 21 and dependent claim 29 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent No. 5,830,500 to El-Rashidy *et al.* ("El-Rashidy"). Applicants respectfully traverse this rejection for the following reason.

The only compositions disclosed by El-Rashidy contain (1) fluoxetine, (2) a disintegrant, (3) dicalcium phosphate dihydrate, and (4) a lubricant. *See, e.g.*, col. 3, lines 38-

40. This disclosure falls outside of claims 21 and 29, and therefore cannot anticipate them. In particular, independent claim 21 recites a tablet "consisting essentially of" fluoxetine or an optically pure enantiomer or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, and pre-gelatinized starch, and thus excludes any "material" ingredients such as the dicalcium phosphate dihydrate of El-Rashidy. MPEP § 2111.03. Therefore, notwithstanding its disclosure of pre-gelatinized starch as a disintegrant, El-Rashidy requires an ingredient which is excluded from claims 21 and 29. As a result, Applicants respectfully request that the rejection of these claims under § 102(e) be withdrawn.

III. The Rejections Under 35 U.S.C. 103(a) Should Be Withdrawn

On pages 2-4 of the Office Action, various claims are rejected under 35 U.S.C. 103(a) as allegedly obvious over El-Rashidy in view of the *Physicians' Desk Reference*, 919-923 (50th ed.; 1996) ("PDR"), WO 97/31629 ("WO '629"), and/or European Patent Application EP 0693281 to Mendizabal ("EPA '281"). Applicants respectfully traverse these rejections for the reasons discussed below.

In order to properly determine a *prima facie* case of obviousness, an Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P. § 2142. This is important, as "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." *Id.*; see also *In re Dembiczak*, 175 F.3d 994, 999 (Fed.Cir. 1999) (holding claims were not obvious over a combination of references that disclosed all of their limitations, but which did not provide a motivation to combine those limitations).

Three basic criteria must then be met: first, there must be some suggestion or motivation to modify or combine the cited references; second, there must be a reasonable expectation of success; and third, the prior art references must teach or suggest all the claim limitations. M.P.E.P. at § 2143. With regard to the first criterion, it is important to recognize that the "mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *Id.* at 2143.01 (emphasis in the original) (citing *In re Mills*, 916 F.3d 680 (Fed. Cir. 1990)). Applicants respectfully submit that all of these criteria have not been met.

A. The Cited References Do Not Disclose or Suggest Compositions or Dosage Forms of an Optically Pure Enantiomer of Fluoxetine

Apart from claims 21 and 29, which are discussed above, all of the claims now pending in this application are directed to pharmaceutical compositions or dosage forms of an optically pure enantiomer of fluoxetine. None of the references cited in the Office Action disclose or suggest such compositions or dosage forms. For example, El-Rashidy only discloses dosage forms of racemic fluoxetine. The Examiner alleges, however, that the PDR "intimates that either one of the enantiomers may be used therapeutically." Relying on *In re Anthony*, 162 USPQ 594 (CCPA 1969) and *In re Adamson and Duffin*, 125 USPQ 233 (CCPA 1960), the Examiner further alleges that "one isomer is expected to be more active than others." Applicants respectfully submit that neither case is applicable to the pending claims.

First, the claims at issue in both *Anthony* and *Adamson* were *compound* claims, not pharmaceutical composition or dosage form claims like those pending here. Second, the *Anthony* court did not determine whether claims that were directed to enantiomers of a known racemic compound were patentable. *Anthony*, 162 USPQ at 596-7. Indeed, the court actually acknowledged that a stereoisomer *may be patentable* over a racemic mixture. *Id.* And third, the decision in *Adamson* was based on a combination of references that reportedly would have motivated one of skill in the art to obtain the claimed *compounds*. *Adamson*, 125 USPQ at 235.

In contrast, the references cited in this case would *not* have motivated one of ordinary skill to obtain the claimed pharmaceutical compositions and dosage forms. For example, the PDR teaches the *exact opposite* of the Examiner's allegation that "isomers of a racemic compounds are expected to have differing activities," by reporting that the pharmacological activities of the (R) and (S) enantiomers of fluoxetine are "essentially equivalent." The PDR thereby provides a *disincentive* to prepare pharmaceutical compositions and dosage forms that contain an optically pure enantiomer of fluoxetine, since it is well known that the separation and purification of enantiomers can be expensive and time-consuming. In view of this fact, Applicants respectfully submit that the rejections of the pending claims over El-Rashidy and the PDR rely on the use of impermissible hindsight. *See, e.g., Interconnect Planning Corp. V. Feil* 774 F.2d at 1138 (An "invention must be viewed not with the blueprint drawn by the

inventor, but in the state of the art that existed at the time.") Applicants therefore respectfully request that all of the rejections of the claims under § 103 be withdrawn.

B. The Cited References Do Not Disclose or Suggest Lactose-Free Dosage Forms of Optically Pure Enantiomers of Fluoxetine

Independent claims 13, 14, 33, and 34 recite dosage forms of an optically pure enantiomer of fluoxetine which are free or substantially free of lactose. As discussed above, none of the cited references disclose or suggest a dosage form of an optically pure enantiomer of fluoxetine. Therefore, none of the cited references disclose or suggest the specific lactose-free dosage forms recited by, for example, claims 13, 14, 33, and 34.

As pointed out on pages 3-4 of the Office Action, El-Rashidy and EPA '281 disclose lists of ingredients which do not include lactose, and which were allegedly used to make tablets of *racemic* fluoxetine. *See, e.g.*, El-Rashidy, col. 4, lines 20-35; EPA '281, page 6, lines 38-54). However, neither reference suggests the preparation of lactose-free dosage forms of optically pure enantiomers of fluoxetine. For example, EPA '281 discloses racemic fluoxetine tablets made with lactose, and describes advantages of using lactose in the preparation of tablets. *See, e.g.*, page 6, lines 10-23; page 3, lines 55-57. El-Rashidy similarly provides no motivation or suggestion to prepare the pharmaceutical compositions and dosage forms of this invention. Indeed, El-Rashidy is silent as to lactose, and does not disclose anything about its effects. Therefore, Applicants respectfully request that the rejection of claims directed to lactose-free compositions of optically pure enantiomers of fluoxetine be withdrawn.

C. The Cited References Do Not Disclose or Suggest Dosage Forms of Optically Pure Enantiomers of Fluoxetine That Dissolve as Recited by Independent Claims 13, 14, and 30

Independent claims 13, 14, and 30 are directed, in part, to dosage forms of an optically pure enantiomer of fluoxetine which dissolve in more than three minutes when subjected to the dissolution test described in the specification. On page 4 of the Office Action, it is alleged that the dosage forms recited by these claims are obvious in view of El-Rashidy and WO '629. Applicants respectfully disagree.

First, neither reference discloses or suggests pharmaceutical compositions or dosage forms of optically pure enantiomers of fluoxetine. For this reason alone, Applicants respectfully submit that the rejection of independent claims 13, 14, and 30 and their dependencies should be withdrawn. Second, while El-Rashidy does allege the measurement of commercially available tablets of *racemic* fluoxetine that dissolve in greater than three minutes, it provides no indication of whether or not those tablets are lactose free.[1] El-Rashidy, col. 5, lines 61-64. This defect is not cured by any of the cited references.

WO '629 is cited on pages 3-4 of the Office Action as evidence that "dissolution time is an art-recognized result-effective variable and it would have been obvious and well within the capability of the skilled artisan to optimize it [to achieve] the compositions of El-Rashidy." Applicants are unable to identify the alleged disclosure on the cited pages of WO '629.[2] However, even if the alleged subject matter was disclosed in the reference, WO '629 would not render claims 13, 14, and 30 obvious, even when combined with El-Rashidy and the PDR. This is because the "mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. at 2143.01 (emphasis in the original) (citing *In re Mills*, 916 F.3d 680 (Fed. Cir. 1990)).

None of the cited references suggest the desirability of the combination of each of the elements recited by independent claims 13, 14, and 30. For example, nothing in any of the references suggests that it is desirable to provide a tablet of an optically pure enantiomer of fluoxetine that dissolves in greater than 3 minutes, much less a lactose-free form of such a tablet. Indeed, El-Rashidy *teaches away* from such tablets by providing tablets that dissolve in only *15 seconds*. El-Rashidy at col. 5, lines 60-61.

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[1] In 1996, when El-Rashidy was filed, the only commercially available dosage form of fluoxetine approved for use in the United States was a capsule. *See, e.g., Physicians' Desk Reference*, pp. 311, 919 (50th ed.; 1996) (enclosed herewith as Exhibit 1). For this reason, Applicants submit that the reference in El-Rashidy to commercially available tablets is likely erroneous; at best, it would have been vague and confusing to one of ordinary skill in the art.

[2] Pages 3 and 4 of WO '629 disclose only the structures of some compounds; they disclose nothing about the dissolution times of particular tablets.

Because there is no suggestion to select and combine various aspects of El-Rashidy, the PDR, and WO '629 to provide the inventions recited by independent claims 13, 14, and 30, it is respectfully submitted that the rejection of these claims and their dependencies is based on the use of impermissible hindsight. *Interconnect Planning*, 774 F.2d at 1138. Applicants respectfully request that the rejection of these claims be withdrawn.

D. The Cited References Do Not Disclose or Suggest Anhydrous Dosage Forms of Optically Pure Fluoxetine

Finally, on page 4 of the Office Action, it is alleged that the anhydrous compositions of this invention are obvious in view of the prior art. Independent claims 23 and 36 are directed, in part, to anhydrous pharmaceutical compositions of an optically pure enantiomer of fluoxetine. As discussed above, none of the cited references disclose or suggest pharmaceutical compositions or dosage forms of an optically pure enantiomer of fluoxetine. For this reason alone, Applicants respectfully submit that the rejection of claims directed to anhydrous compositions of an optically pure enantiomer of fluoxetine be withdrawn. Other reasons also exist for the withdrawal of this rejection.

For example, El-Rashidy provides no indication that the tablets of racemic fluoxetine it discloses are anhydrous or substantially free of water. As those of ordinary skill in the art are well aware, the fact that an ingredient used in a process is reportedly "dry" does not mean that it is anhydrous (*i.e.*, free or substantially free of water). This fact is exemplified by El-Rashidy itself, which states that the ingredients used to make the tablet of Example 1 were "dry," even though one of the ingredients used in that process (dicalcium phosphate dihydrate) contains water. Col. 3, line 63 - col. 4, line 34. For this reason, Applicants respectfully disagree with the Examiner's characterization of the process disclosed by El-Rashidy as a "dry process" that will remove water from the ingredients used therein so as to yield anhydrous tablets: Applicants are unable to find any disclosure or suggestion in El-Rashidy that the process disclosed therein would remove water trapped in the ingredients used in it.[3]

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[3] If the Examiner's conclusion is based on knowledge not expressly disclosed in the cited references, Applicants respectfully request that she set forth the facts upon which her conclusion is based in an affidavit under 37 C.F.R. § 1.104(d)(2).

None of the other references cited by the Examiner disclose or suggest an anhydrous pharmaceutical composition of an optically pure enantiomer of fluoxetine. Therefore, it is respectfully requested that the rejection of claims directed to anhydrous pharmaceutical compositions and dosage forms be withdrawn.

D. Conclusion

Applicants respectfully submit that the rejections based on §§ 112 and 102 have been obviated by the amendments provided herein, and that the rejections under § 103 should be withdrawn. All of the claims are believed to be in condition for allowance. Should the Examiner deem it helpful, a personal or telephone interview is respectfully requested to discuss any remaining issues.

No fee is believed to be due for this submission. However, if a fee is due, please charge it to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: January 3, 2002

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Enclosures

ATTACHMENT A

MARKED-UP VERSION OF AMENDMENTS

Please amend claim 23 as follows:

23. (Amended) An anhydrous solid pharmaceutical composition which comprises [racemic fluoxetine,] an optically pure enantiomer of [racemic] fluoxetine or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

ATTACHMENT B

PENDING CLAIMS

1. A lactose-free pharmaceutical composition which comprises an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof, and at least one non-lactose pharmaceutically acceptable excipient.

2. A solid pharmaceutical composition which comprises an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein said excipient is not lactose.

3. The composition of claim 1, wherein said non-lactose pharmaceutically acceptable excipient is a binder, a filler, or a mixture thereof.

4. The composition of claim 2, wherein said pharmaceutically acceptable excipient is a binder, a filler, or a mixture thereof.

5. The composition of claim 3 or 4 wherein said binder is a starch.

6. The composition of claim 3 or 4 wherein said binder is a cellulose.

7. The composition of claim 5 wherein said starch is selected from the group consisting of corn starch, potato starch, pre-gelatinized starch and a mixture thereof.

8. The composition of claim 6 wherein said cellulose is selected from the group consisting of ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, microcrystalline cellulose and a mixture thereof.

9. The composition of claim 3 or 4, which further comprises a lubricant, disintegrant, or mixtures thereof.

10. The composition of claim 1 or 2, wherein said enantiomer of fluoxetine is (R)-fluoxetine.

11. The composition of claim 1 or 2, wherein said enantiomer of fluoxetine is (S)-fluoxetine.

12. The composition of claim 1 or 2, wherein said pharmaceutical composition is substantially free of all mono- or di-saccharides.

13. A chemically stable compressed tablet free of lactose which comprises an optically pure enantiomer of fluoxetine or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, wherein said tablet does not dissolve in less than three minutes when subjected to the DISSOLUTION TEST.

14. A chemically stable compressed tablet free of lactose which comprises about 1% to about 50% by weight of an optically pure enantiomer or a pharmaceutically acceptable salt thereof, and about 99% to about 50% by weight of at least one pharmaceutically acceptable excipient, wherein said tablet does not dissolve in less than three minutes when subjected to the DISSOLUTION TEST.

15. The compressed tablet of claims 13 or 14 wherein said tablet does not contain a disintegrant.

16. The compressed tablet of claim 13 or 14 wherein said tablet dissolves and disperse uniformly in more than five minutes when subjected to the DISSOLUTION TEST.

17. The compressed tablet of claim 13 or 14, wherein said fluoxetine is present in an amount from about 1 mg to about 200 mg.

18. The compressed tablet of claim 17, wherein said fluoxetine is present in an amount of about 2 mg to about 100 mg.

19. The compressed tablet of claim 13 or 14, wherein said fluoxetine enantiomer is optically pure (R)-fluoxetine.

20. The compressed tablet of claim 13 or 14, wherein said fluoxetine enantiomer is optically pure (S)-fluoxetine.

21. A stable, solid compressed tablet consisting essentially of racemic fluoxetine, or an optically pure enantiomer or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose and pre-gelatinized starch.

22. The compressed tablet of claim 13 or 14, wherein said compressed tablet is sterile, anhydrous and non-hygroscopic.

23. An anhydrous solid pharmaceutical composition which comprises an optically pure enantiomer of fluoxetine or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

24. The composition of claim 23 wherein said composition does not contain lactose.

25. The composition of claim 23 or 24 wherein said composition is a compressed tablet.

26. The composition of claim 23 or 24 wherein said fluoxetine enantiomer is optically pure (R)-fluoxetine.

27. The composition of claim 23 or 24 wherein said fluoxetine enantiomer is optically pure (S)-fluoxetine.

28. The composition of claim 23 or 24 wherein said composition is non-hygroscopic.

29. The composition or tablet of claim 1, 13, 14, 21, 23, or 24 wherein said pharmaceutically acceptable salt is a hydrochloride salt.

30. A stable pharmaceutical unit dosage form which comprises an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof, and one of more pharmaceutically acceptable excipients wherein said dosage form is not a capsule or gel cap and does not dissolve in less than three minutes when subjected to the DISSOLUTION TEST.

31. The unit dosage form of claim 30 wherein said fluoxetine enantiomer is optically pure (R)-fluoxetine.

32. The unit dosage form of claim 30 wherein said fluoxetine enantiomer is optically pure (S)-fluoxetine.

33. A solid compressed tablet substantially free of lactose which comprises an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient which is not lactose.

34. A disintegrating tablet substantially free of lactose which comprises an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient which is not lactose.

35. A method of treating depression in a mammal which comprises the oral administration of a therapeutically effective amount of a composition or tablet of claim 1, 2, 13, 14, 21, 23, 24, 30, 33 or 34 to said mammal.

36. An anhydrous or non-hygroscopic pharmaceutical composition consisting essentially of an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient, wherein the composition is substantially free of unbound water.

37. The compressed tablet of claim 21 wherein said tablet dissolves in more than five minutes when subjected to the DISSOLUTION TEST.